Medical Pharmacology

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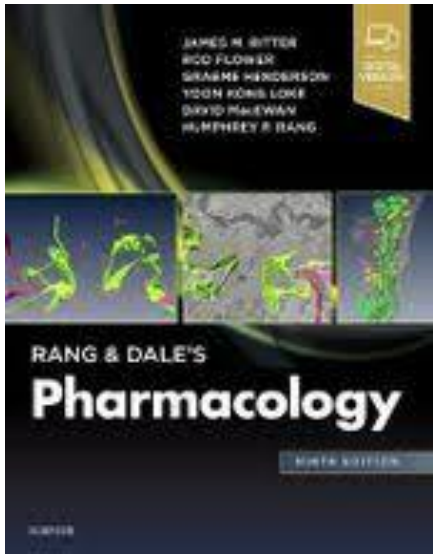
JAMES COOK UNIVERSITY AUSTRALIA

Celebrating 50 YEARS 1970 - 2020

Gastrointestinal Pharmacology

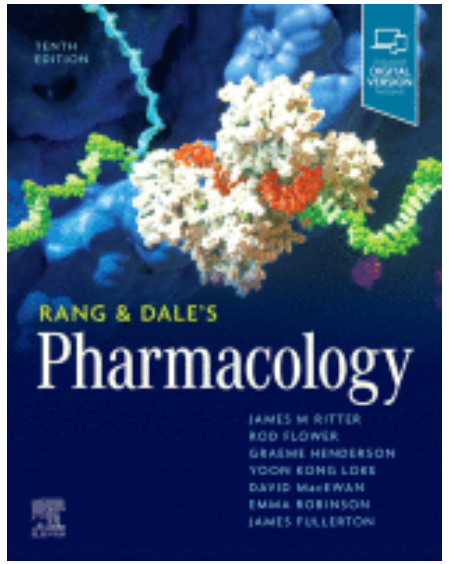
Lecture 3 – pharmacological agents for nausea & vomiting



Rang & Dale's Pharmacology

9th edn 2020

Chaps 31, 33



Rang & Dale's Pharmacology

10th edn 2023

Chaps 30, 32

Learning Objectives

By the end of this module, students should be able to demonstrate and apply knowledge of:

- Mechanisms of emesis
- Pharmacology of antiemetic agents (for nausea and vomiting)
    1. Anticholinergics/Antimuscarinics
    2. H1 receptor antagonists/Sedating antihistamines
    3. Dopamine D_2 receptor antagonists
    4. Serotonin 5-HT_3 antagonists
    5. NK1 receptor antagonists

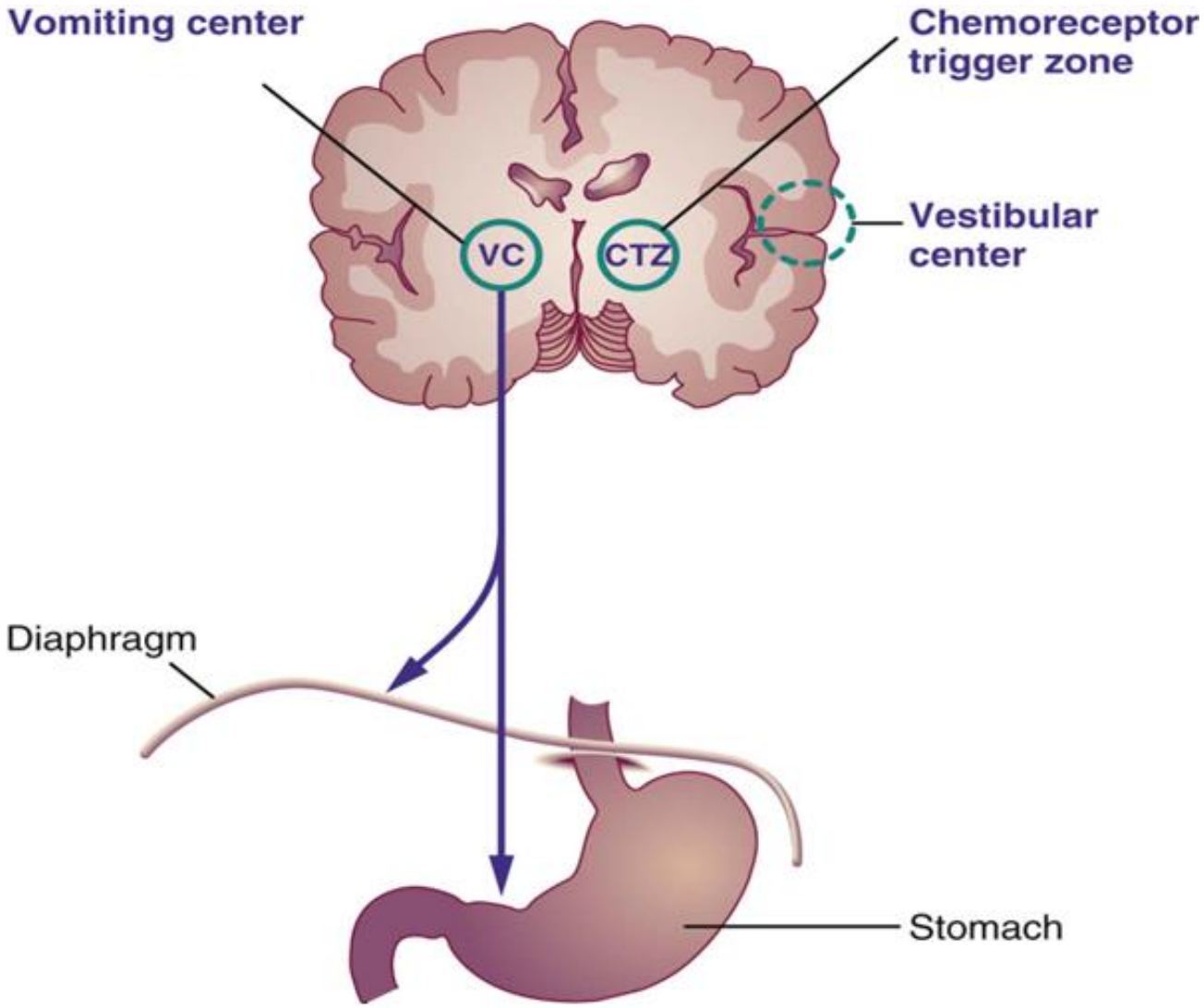
Emesis

Emesis (vomiting) is the forceful expulsion of the contents of the stomach (and sometimes intestines) through the mouth.

It's a protective mechanism to rid upper GIT of contents

Mechanisms involve:

- Chemoreceptor Trigger Zone (CTZ)
- Vomiting Center
- Vestibular System
- Vagal/Visceral Afferents



Causes and mechanisms of nausea and vomiting

- occurs when the upper GIT becomes excessively irritated, distended
- consequences include dehydration, malnutrition, vitamin deficiency, metabolic alkalosis etc
- Ingestion of toxin/bacteria (eg gastroenteritis)
  - Stimulation of Serotonin or Substance P from ECC cells in gastric lining ->CTZ -> VC

- Damage to stomach lining/viscera (eg surgery) or mechanical stimulation in GIT (eg pressure or fullness)
  - Stimulation of Serotonin or Substance P from ECC cells in gastric lining -> CTZ -> VC

- Emetic agents (drugs) (eg cytotoxic agents used in chemotherapy, Ipecac, Levodopa, Digoxin, opioids, ergot alkaloids
  - Multiple mechanisms including ECC, CTZ, 5HT3, D2 receptor stimulation

- Absorbed toxins
  - Can stimulate CTZ directly (outside the BBB)

The Chemoreceptor Trigger Zone (CTZ):

- Vomiting is regulated by the vomiting centre and the chemoreceptor trigger zone (CTZ)
- CTZ - located in the area postrema, in the medulla oblongata and lies outside the BBB
- CTZ regulates motion sickness and is main site of action of many emetic and antiemetic drugs

- Receives input from:
  - Circulating toxins/chemicals in the CSF and blood
    - endogenous and exogenous substances
    - mediators, hormones, toxins and drugs
  - Vagal (visceral) afferents- take the signal from the GIT to the brain stem
  - Vestibular system

- Cannot trigger the vomiting reflex directly.

- Many receptor types:
  - *Dopamine D2 receptors, 5-HT receptors*
  - Also, adrenoceptors, muscarinic, histamine, opioid and substance P receptors.

The Vomiting Centre:

- Diffused organisation of neurons scattered throughout the medulla
- controls visceral and somatic functions involved in vomiting

- Receives information from:
  - CTZ
  - Vagal (visceral) afferents
  - Vestibular system.
  - Higher centres in the brain
    - sights, smells, tastes, emotional factors, pain and memory.

- Activation of the receptors in the vomiting centre can trigger the vomiting reflex.

- Many receptor types:
  - Muscarinic receptor, opioid receptor, cannabinoid CB1 receptor, a2-adrenoceptor (noradrenaline), D2 receptor, 5-HT3 and 5-HT4 receptors, Neurokinin NK1 receptor.

The Vestibular System:

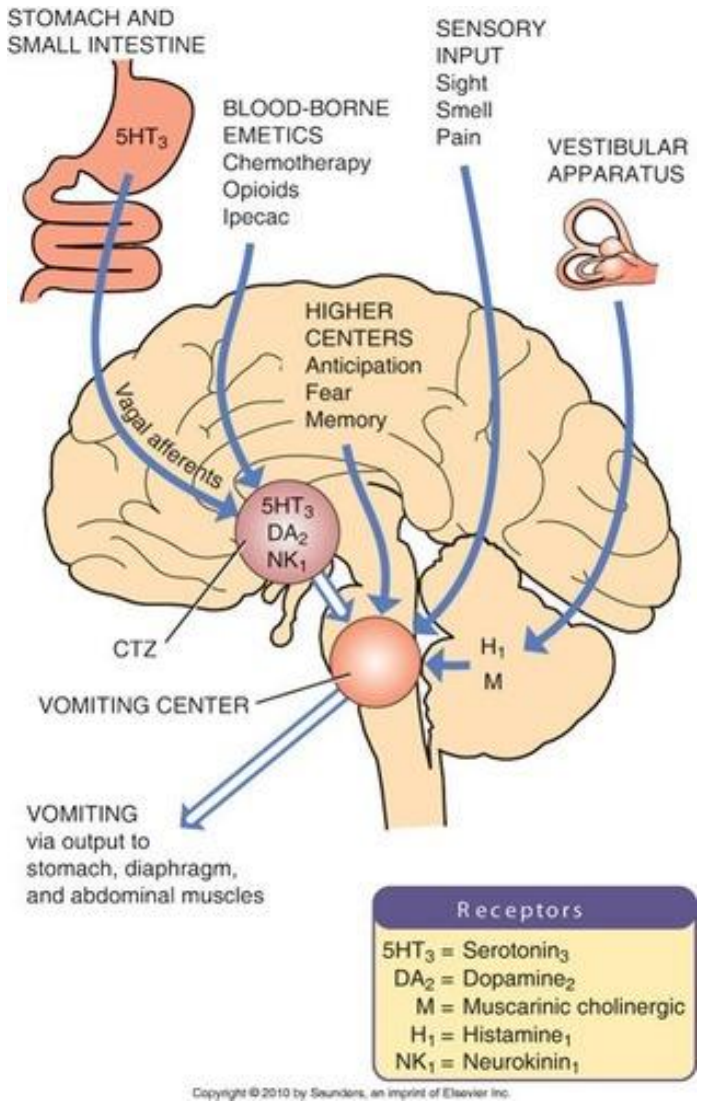
- The vestibular system in the inner ear primarily functions to detect head motion and position relative to gravity (balance).
- Stimulation of the labyrinth in the inner ear leads to impulses passing along the vestibulocochlear nerve to the vestibular nuclei in the brainstem, to receptors in the CTZ and the VC.
- Involved in motion sickness causing nausea and vomiting.
- Receptor types:
  - *Muscarinic receptors and Histamine (type 1) receptors*

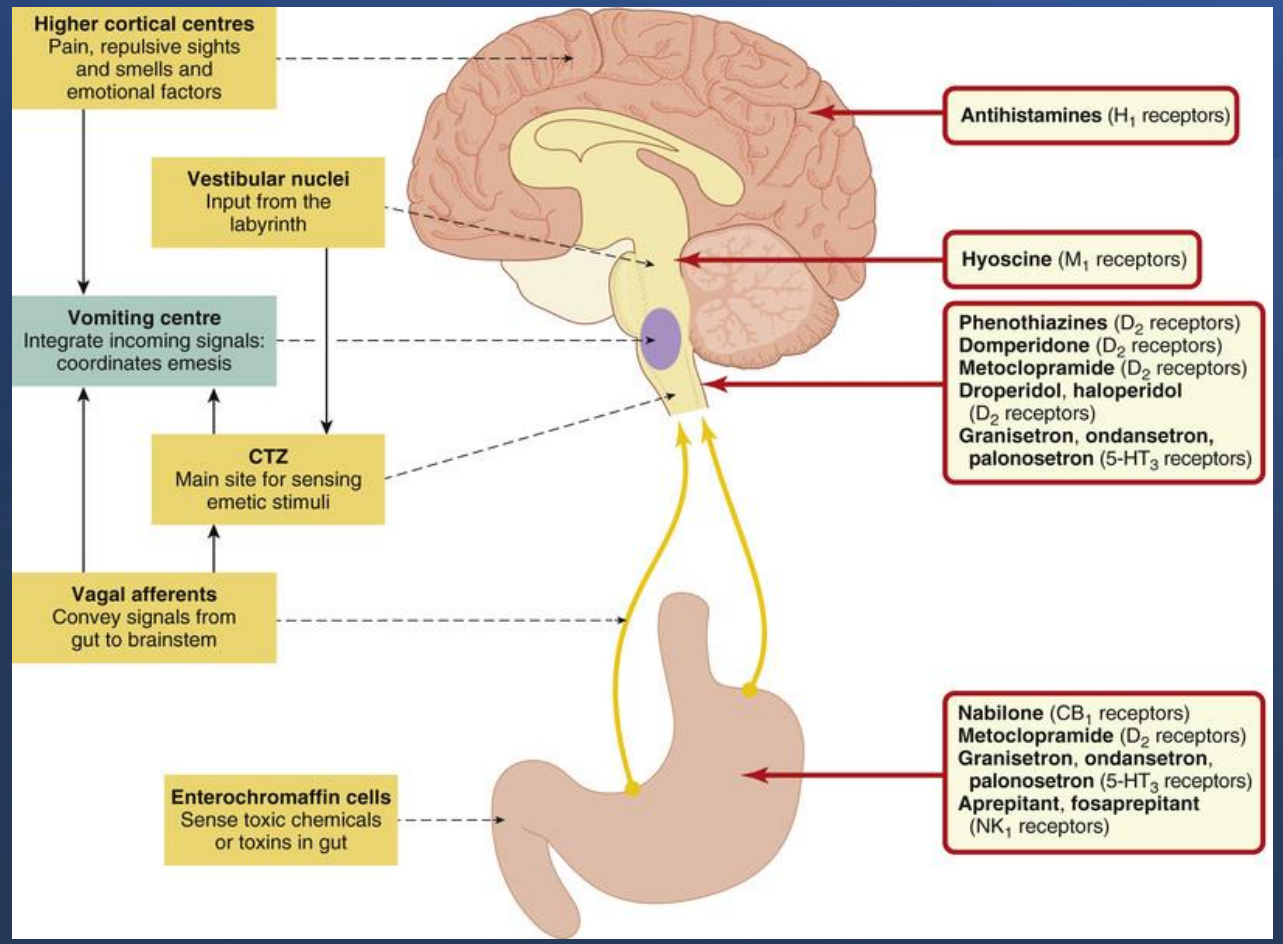
Vagal Afferents:

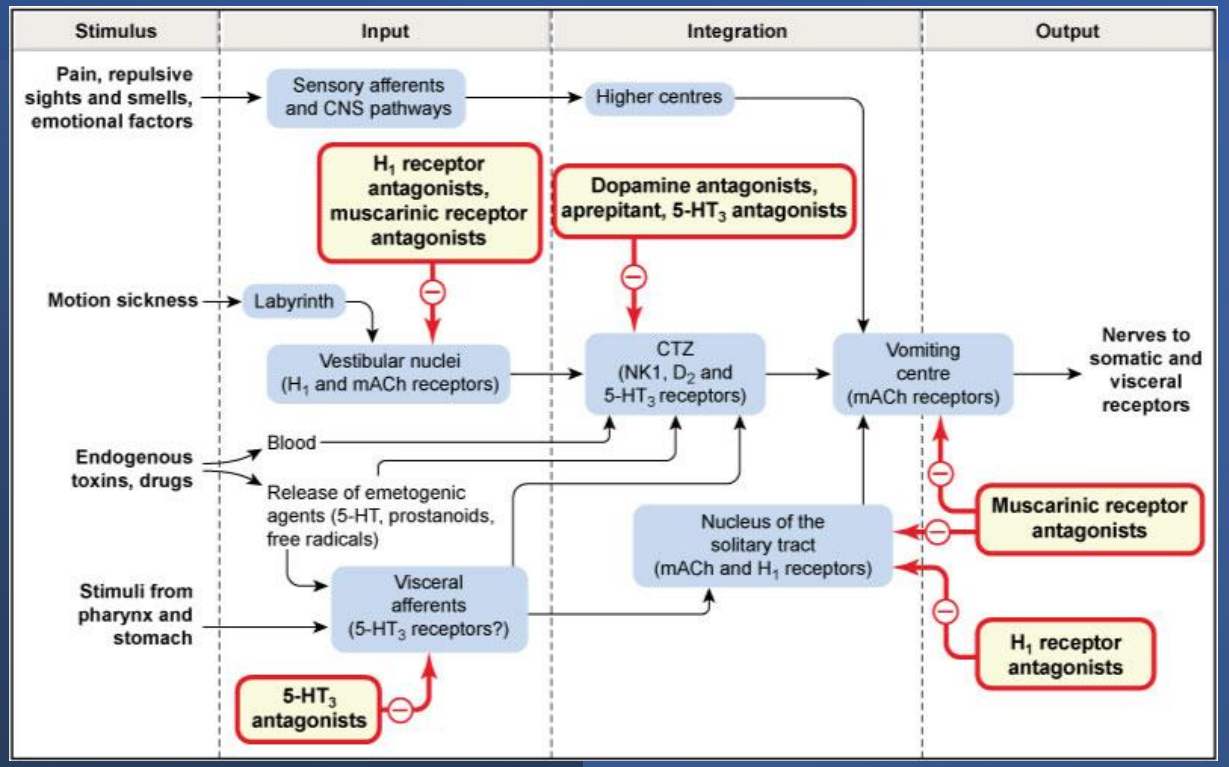
- Enterochromaffin cells (ECC) in gastric lining release 5-HT and/or substance P in response to toxins
- Vagal afferents allow signals from the viscera to the CNS (CTZ and vomiting centre).
- Receptor types:
  - *5-HT and Neurokinin NK1/substance P*

Emesis

- The VC can induce emesis.
- Efferent impulses are sent from the vomiting centre to the upper GIT, diaphragm and abdominal muscles.
- The contraction of stomach muscles, the movement of stomach contents up the oesophagus, past the oesophageal sphincter and into the mouth results in vomiting.
- Salivation, sweating, rapid breathing and cardiac dysrhythmias- mediated by SNS and PNS.




Higher cortical centres
Pain, repulsive sights and smells and emotional factors
Vestibular nuclei
Input from the labyrinth
Vomiting centre
Integrate incoming signals: coordinates emesis
CTZ
Main site for sensing emetic stimuli
Vagal afferents
Convey signals from gut to brainstem
Enterochromaffin cells
Sense toxic chemicals or toxins in gut
Antihistamines (H_1 receptors)
Hyoscine (M_1 receptors)
Phenothiazines (D_2 receptors)
Domperidone (D_2 receptors)
Metoclopramide (D_2 receptors)
Droperidol, haloperidol (D_2 receptors)
Granisetron, ondansetron, palonosetron ($5\text{-}HT_3$ receptors)
Nabilone (CB_1 receptors)
Metoclopramide (D_2 receptors)
Granisetron, ondansetron, palonosetron ($5\text{-}HT_3$ receptors)
Aprepitant, fosaprepitant (NK_1 receptors)


Stimulus
Input
Integration
Output
Pain, repulsive sights and smells, emotional factors
Sensory afferents and CNS pathways
Higher centres
H_1 receptor antagonists, muscarinic receptor antagonists
Dopamine antagonists, aprepitant, $5\text{-}HT_3$ antagonists
Motion sickness
Labyrinth
Vestibular nuclei (H_1 and mACh receptors)
CTZ (NK1, D_2 and $5\text{-}HT_3$ receptors)
Vomiting centre (mACh receptors)
Nerves to somatic and visceral receptors
Endogenous toxins, drugs
Blood
Release of emetogenic agents (5-HT, prostanoids, free radicals)
Nucleus of the solitary tract (mACh and H_1 receptors)
Muscarinic receptor antagonists
Stimuli from pharynx and stomach
Visceral afferents ($5\text{-}HT_3$ receptors?)
H_1 receptor antagonists
$5\text{-}HT_3$ antagonists

Neurotransmitters and Receptors

The pharmacology of antiemetics is based on blocking the actions of neurotransmitters involved in the mechanisms of emesis.

- Acetylcholine- M_1 receptors
- Histamine - H_1 receptors
- Dopamine - D_2 receptors
- Serotonin (5-hydroxytryptamine) - $5HT_3$ receptors
- Substance P - NK_1 receptors

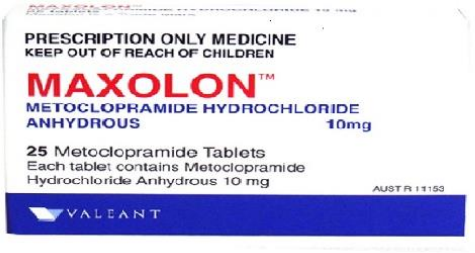
1. Anticholinergics/Antimuscarinics

- Examples include hyoscine hydrobromide (don't confuse with hyoscine butylbromide!)
- Used to prevent and treat motion sickness
- Competitive antagonist of the actions of Ach at muscarinic receptors
- Anticholinergic actions on M1 in the vestibular nuclei and possibly elsewhere.
- Hyoscine hydrobromide crosses the blood brain barrier and CNS side effects such as dry mouth, dizziness and blurred vision limit patient acceptance.

2. H1 Receptor Antagonists/ Sedating Antihistamines

- Examples include promethazine, dimenhydrinate and cyclizine.
- Block Histamine H_1 receptors in the CNS and possibly anticholinergic actions in the vestibular apparatus.
- Used to prevent and treat vomiting associated with motion sickness and morning sickness.
- Not very effective against substances that act directly on the CTZ.
- Anticholinergic side effects of sedating antihistamines such as dry mouth, dizziness, drowsiness, dry eyes, and blurred vision may limit use.

3. Dopamine D_2 Receptor Antagonists



- Prochlorperazine, haloperidol, metoclopramide and domperidone.
- Short term use advised- risk of EPSE
- **Prochlorperazine** blocks D_2 receptors in the CTZ and blocks H_1 and muscarinic receptors. Used for N&V caused by migraine, vestibular disorders (vertigo), radiation, viral gastroenteritis and morning sickness.
- **Metoclopramide** blocks central D_2 receptors in the CTZ and peripheral D_2 receptors in the GIT. Used for nausea and vomiting caused by migraine, radiation, gastrointestinal disorders, cytotoxic drugs and surgery. Exerts prokinetic activity – increase gastric emptying.
- **Domperidone**- a dopamine antagonist (D2 and D3) that is hydrophyllic, does not cross the blood–brain barrier- CNS effects are rare. Rarely causes EPSE and is the anti-emetic of choice in Parkinson's disease. Also exerts prokinetic activity.
- Caution/Adverse effects
  - caution in Parkinson's disease, depression
  - motor restlessness, drowsiness, dizziness, headache

4. Serotonin $5HT_3$ Receptor Antagonists

- Examples include ondansetron, granisetron, palonosetron and tropisetron.
- Blocks central 5-HT_3 receptors in the CTZ, CNS and blocks peripheral 5-HT_3 receptors on vagal nerve terminals.
- Used to prevent or treat nausea and vomiting associated with chemotherapy, radiation or surgery (manipulation of the viscera).
- Side effects include constipation, headache, dizziness.

5. NK_1 Receptor Antagonists

- Also known as substance P antagonists.
- Examples include aprepitant and fosaprepitant.
- Aprepitant blocks NK_1 receptors (GPCRs) in the CTZ and vomiting centre, and the GIT.
- Used to prevent severe nausea and vomiting associated with emetogenic chemotherapy
- Often co-administrated with 5-HT_3 antagonists and dexamethasone (a corticosteroid).

- **Adverse effects / Precautions / Interactions**
  - diarrhoea, fatigue, hiccups !
  - hormonal contraception
    - - use alternative or back-up methods
  - inhibits CYP3A4 and induces CYP2D6